

**Protocol Title:** Randomized Clinical Trial of Streaming Dichoptic Movies versus Patching for Treatment of Amblyopia in Children Aged 3 to 7 Years

**Date:** January 31, 2019

**clinicaltrials.gov identifier:** NCT03825107

**Financial support:** National Institutes of Health Grant EY022313 (Birch, PI)

Principal Investigator: Eileen E Birch, PhD  
Senior Research Scientist  
Pediatric Vision Laboratory  
Retina Foundation of the Southwest  
9600 North Central Expressway, Suite 200  
Dallas, TX 75231  
phone: (214) 363-3911  
email: ebirch@retinafoundation.org

**Single site study conducted at:** Retina Foundation of the Southwest  
9600 North Central Expressway, Suite 200  
Dallas, TX 75231

## **Project Summary**

Contrast-rebalanced dichoptic movies (with fellow eye contrast reduced) have been shown to be an effective binocular treatment for amblyopia in a laboratory setting. Yet, at-home therapy is a more practical approach. While contrast-rebalanced binocular tablet games have been shown to be an effective at-home treatment for amblyopia, the games can be challenging for some of the youngest children with amblyopia. To address this need, we will compare dichoptic movies, streamed at-home on a handheld 3D-enabled game console, versus patching as amblyopia treatment for children aged 3 to 7 years with amblyopia. The primary outcome will be change in best-corrected acuity at the 2-week visit in children treated with streaming dichoptic movies versus children treated with standard-of-care 2 hours/day patching. A secondary objective is to determine whether amblyopic eye visual acuity improvement at the 2-week visit is significant in each of the treatment groups. Fifty-six amblyopic children (aged 3-7 years) will be randomly assigned to patching (2 hours/day, 7 days/week; 28 hours total) or binocular treatment (3 dichoptic movies per week; 9 hours total). In the context of prior amblyopia treatment results with at-home contrast-rebalanced tablet games and with in-lab contrast-rebalanced movies, we anticipate that dichoptic movies, streamed at-home on a handheld 3D-enabled game console will be more effective than patching.

## **Rationale and background**

Contrast-rebalanced binocular tablet games (with fellow eye contrast reduced) have been shown to be an effective treatment for amblyopia.<sup>1,2</sup> However, the games can be challenging for some of the youngest children and boring for some of the older children

with amblyopia. To provide additional treatment options using the same contrast-rebalancing approach, we have processed animated videos to allow dichoptic viewing, with full contrast for the amblyopic eye and reduced contrast for the fellow eye. In prospective single-arm studies, contrast-rebalanced dichoptic movies have been used as an effective treatment for children aged 4 to 12 years with amblyopia.<sup>3</sup> With as little as 9 hours of viewing time, mean improvement of visual acuity of the amblyopic eyes was 1.5 to 2.0 lines.<sup>4,5</sup> There is evidence that younger children ( $\leq 7$  years) are more responsive to amblyopia treatments,<sup>6,7</sup> including treatment with contrast-rebalanced dichoptic movies, than older children.<sup>4</sup> While in-lab studies of amblyopia treatment with contrast-rebalanced dichoptic movies provided proof-of-principle data for the treatment approach, at-home treatment is a more practical alternative.

### **Study Goal**

To explore an at-home amblyopia treatment in younger children with contrast-rebalanced dichoptic movies.

### **Objective**

In a randomized clinical trial, we plan to evaluate the effectiveness of viewing cloud-based contrast-rebalanced dichoptic movies streamed on a handheld device in children aged 3 to 7 years compared with standard-of-care patching treatment.<sup>8</sup>

### **Methodology**

Children aged 3 to 7 years who are diagnosed by pediatric eye specialists as having amblyopia due to strabismus, anisometropia, or both (combined mechanism) are eligible. Diagnoses, alignment, prior treatment, and visual acuity for visits prior to enrollment will be extracted from the referring doctor's medical records.

#### *Inclusion criteria*

- Amblyopic eye visual acuity of 0.2 to 0.8 logMAR
- Fellow eye visual acuity of  $-0.1$  to  $0.2$  logMAR
- Interocular visual acuity difference of  $>0.2$  logMAR
- Anisometropia or corrected strabismus ( $<5$ pd)
- Wearing glasses for at least 8 weeks with no change in visual acuity over two visits
- Must be able to see the full movie screen (both amblyopic and fellow eye components) with fellow eye contrast set to 20%.

#### *Exclusion criteria*

- Prematurity of 8 weeks or more
- Coexisting ocular or systemic disease
- Developmental delay
- Significant ocular misalignment ( $\geq 5$  pd).

#### *Study Design*

This study is a randomized clinical trial (parallel group design). At the baseline visit, eligibility will be ascertained and vision assessments conducted. Children will be randomly assigned to watch contrast-rebalanced dichoptic animated movies

(experimental treatment) or to patch the fellow eye 2 hours/day every day (standard-of-care amblyopia treatment) for 2 weeks. Randomization will be performed through the website [www.randomization.org](http://www.randomization.org) with a coded distribution of a 1:1 ratio, with blocks of 12 allocations. Investigators will have access to the randomization assignment (sealed in a numbered envelope) only after the child is enrolled.

At the 2-week primary outcome visit, children in the patching group will cross over to the dichoptic animated movie group and all participants will be asked to return for a secondary outcome visit vision assessment at 4 weeks. After that, children in the dichoptic movie group will have the option to continue an additional 2 weeks and children who were initially in the patching group will have the option to continue with movies for an additional 4 weeks (up to 6 weeks of movies for both groups). Children who continue will have follow-up visits with vision assessments every 2 weeks ( $14 \pm 3$  days).

### *Dichoptic Movies*

Eighteen popular animated feature films were modified using custom MATLAB software to allow dichoptic presentation on a New Nintendo 3DS XL platform (Nintendo Corporation, Kyoto, Japan), which will be loaned to the child for the duration of the study so that movies can be watched at home. This Nintendo device allows for dichoptic viewing without the need for anaglyphic, polarized, or shutter glasses or a VR headset. The movies have the same design as in our recent prospective study of contrast-rebalanced movies in which children came into the laboratory to watch movies on a passive 3D display.<sup>4,5</sup> Briefly, odd lines in the Nintendo 3D display are visible to one eye, and even lines are visible to the other eye. A patterned image mask composed of irregularly shaped blobs was multiplied with the images seen by the amblyopic eye, and the inverse patterned mask was multiplied with the images seen by the fellow eye, so that different parts of the display are seen by each eye. Blobs of the movie seen by the amblyopic eye always have high contrast (100%), whereas the complementary blobs seen by the fellow eye have reduced contrast. Because the blobs had Gaussian edges, the edges of the blobs overlap and are seen by both eyes with differing contrasts, preventing any significant rivalry. The shape and location of the blobs are varied dynamically every 10 seconds. Fellow eye contrast starts at 20% for the first movie and increments by 10% for each subsequent movie (i.e., 20%, 22%, 24%, 26%, 29%, ...). Movies have been uploaded to our Amazon Web Services (AWS; Seattle, WA, USA) streaming service in two-week packets, each containing 6 movies that preserve the order of fellow eye contrasts from low to high.

### *Study Protocol*

Children allocated to the dichoptic movie arm will be asked to watch 3 movies per week (about 4.5 hours per week) during each 2-week period. During their visit, we will provide a link on their loaned Nintendo for the set of 6 movies that should be watched during the next two weeks. Movie names are numbered on the Nintendo device, in order by fellow eye contrast, and the family will be instructed that the movies should be viewed in that order at home with the date recorded on a paper calendar. Fellow eye contrast of movies 1-6 increment from 20% to 32% during the first 2 weeks, movies 7-12 increment

from 35% to 57% during weeks 3 and 4 and, finally, movies 13-18 increment from 63% to 100% if children participate in the optional weeks 5 and 6. Children allocated to the patching arm will be supplied with patches and asked to patch two hours per day for two weeks. At the 2-week visit, children in the patching group will be loaned a Nintendo and begin watching movies, starting with 20% fellow eye contrast for the next two weeks, and have the option of completing up to 6 weeks of movies.

### *Vision Assessments*

Visual acuity. Crowded monocular best-corrected visual acuity (BCVA) will be tested at each visit using the Amblyopia Treatment Study HOTV protocol for 3- to 6-year olds<sup>9-11</sup> and the E-ETDRS protocol for 7-year olds.<sup>12,13</sup>

Stereoacuity. Stereoacuity will be assessed with the Randot Preschool Stereoacuity Test and the Stereo Butterfly Test; stereoacuity will be converted to log arcsec for analyses; nil stereoacuity will be arbitrarily assigned a value of 4.0.<sup>14</sup>

Suppression. Extent of suppression will be assessed using the Worth-4 dot test at 7 distances (3m, 2m, 1m, 0.67m, 0.5m, 0.33 m, and 0.16m); the farthest distance at which the child reports 4 dots will be converted to the area of suppression scotoma in log degrees.<sup>15</sup> Depth of suppression will be evaluated using a dichoptic eye chart that identifies the non-preferred eye/preferred eye contrast ratio (i.e., balance point) at which the child can overcome suppression and report letters presented to each eye with equal likelihood (Contrast Balance Index; CBI).<sup>16,17</sup>

### **Sample Size**

Based on our recent prospective study of contrast re-balanced dichoptic movies as a treatment for amblyopia,<sup>4,5</sup> we anticipate a  $0.15 \pm 0.10$  logMAR (7.5 letters) improvement in visual acuity at the 2-week primary outcome visit for children assigned to the dichoptic movie arm. For children assigned to the patching group, we anticipate a  $0.07 \pm 0.10$  logMAR (3.5 letters) improvement at 2 weeks based on results from our prior study of patching versus a contrast-rebalanced dichoptic game as a treatment for amblyopia.<sup>2</sup> With these expected means, a sample size of 28 per group (56 total) will provide 85% power to declare that the two groups have significantly different means, using a two-sided p-value of less than 0.05. We will enroll and randomize 62 children (31 per group) to account for potential 10% loss to follow-up.

### **Expected Outcomes**

Results will be disseminated at the annual meetings of the Association for Pediatric Ophthalmology & Strabismus and the Association for Research in Vision & Ophthalmology and submitted for publication in a leading medical/scientific journal.

If this novel at-home binocular movie treatment is effective in improving amblyopic eye visual acuity, it will provide an additional treatment option for amblyopia in young children.

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